REMARKS

Claims 7-9 and 13 are pending in the subject application. By this Amendment, applicants have added new claims 14-25. Applicants note that new claims 14-23 are fully supported, *inter alia*, in the specification as follows: Claim 14: page 21, lines 5-6; page 26, line 34 to page 27, line 7; page 60, lines 7-24; Table 3; page 63, Table 4 and line 2 to page 64, line 5; Claim 15: page 26, line 34 to page 27, line 7; page 60, lines 7-24; page 61, Table 3; Claims 16-18: page 26, line 34 to page 27, line 7; Claim 19: page 63, Table 4 and line 2 to page 64, line 5; Claim 20: page 19, line 12 to page 21, line 6; pages 60-64; Claim 21: page 26, line 34 to page 27, line 7; page 60, lines 7-24; page 61, Table 3; Claims 22-24: page 26, line 34 to page 27, line 7; and Claim 25: page 63, Table 4 and line 2 to page 64, line 5. Thus, applicants maintain that the addition of new claims 14-25 does not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 7-9 and 13-25 will be pending and under examination.

Applicants again thank the Examiner for the courtesy extended during the interview held on December 7, 2004, a Summary of which was prepared by the Examiner on December 7, 2004 and a Communication regarding which was filed by applicants on December 23, 2004.

The Invention

The claimed invention provides a method of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1. This method comprises contacting the CD4+ cell with an agent which is capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but not capable of inhibiting fusion of HeLa-env_{LAI} to a

HeLa-CD4+ cell, so as to thereby inhibit the fusion of the macrophage-tropic primary isolate of HIV-1 to the CD4+ cell. In embodiments of this invention, the agent may be a protein moiety or a non-protein moiety. Examples of protein moieties include antibodies, such as monoclonal antibodies, and β-chemokines.

Rejections under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claims 7-9 and 13 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (citing *In re Rasmussen,* 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981); *In re Wertheim,* 541 F.2d 257, 191 U.S.P.Q. 90 (C.C. P.A. 1976)). The Examiner stated that the claims are directed toward methods of inhibiting macrophage-tropic HIV-1 fusion to a $CD4^+$ cell target through the administration of an "agent" that inhibits HIV-1 macrophage-tropic fusion events without inhibiting HIV-1 T-cell tropic fusion events. The Examiner also stated that the disclosure describes a fluorescent resonance energy transfer (FRET) assay that is useful for studying membrane fusion events mediated by the HIV-1 envelope. The Examiner further stated that preliminary evidence suggests that certain β-chemokines (e.g., MIP-1α) may inhibit primary, NSI, Env fusion interactions without affecting SI fusion events. The Examiner additionally stated that this interaction, however, appeared to be cell-dependent. The Examiner also stated that another inhibitory molecule (e.g., OKT4A) was non-specific and inhibited both NSI- and SI-Env-mediated events. The Examiner asserted that the claims encompass a large genus of poorly defined chemical compounds which could include, *inter alia*, antibodies, organic compounds, small molecular weight

polypeptides, peptidomimetics, and retroinverso peptides.

The Examiner also stated that to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (citing, e.g., *Vas-Cath, Inc., v. Mahurkar,* 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116). According to the Examiner, the issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of "agents" that display preferential inhibitory activities toward NSI-Env-mediated events but not SI-Env-mediated events. The Examiner stated that, as set forth *supra*, this genus has no structural boundaries and could encompass, *inter alia*, antibodies, organic compounds, small molecular weight polypeptides, peptidomimetics, and retroinverso peptides.

The Examiner stated that an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations, using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth the claimed invention (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997)). The Examiner noted that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. The Examiner also stated that a biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest (citing *In re Bell,* 991

F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993); *In re Deuel,* 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995)). The Examiner further stated that an issue of a lack of adequate written description also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process (citing e.g., *Fujikawa v. Wattanasin,* 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995)). The Examiner stated that the court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

The Examiner stated that an applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. The Examiner further stated that an applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The Examiner also stated that for some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The Examiner additionally stated that the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. The Examiner also stated that without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely.

The Examiner further stated that in the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement (citing *Regents of the University of California v. Eli Lilly,* 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1089 (1998), *In re Wilder,* 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984)). The Examiner noted that factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

In response, applicants respectfully traverse this "written description" rejection for the reasons set forth below.

Applicants reiterate the Examiner's statements that an applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, including, *inter alia*, 1) binding specificity, 2) functional characteristics alone or coupled with a known or disclosed correlation between function and structure, and 3) the method of making the claimed invention. In this regard, applicants note that the specification discloses a method (the RET assay) for identifying agents with the properties specified in the claims. In addition, applicants assert that the binding specificity of the agent and its capability, as recited in the pending claims, to inhibit fusion of HIV-1 to one type of cell but not to another, are identifying characteristics of the agent. Applicants further assert that the capability of the agent to bind to the target cell is a function of the agent. Moreover, applicants assert that there is clearly a correlation between the function and the identifying characteristics of the agent.

Accordingly, applicants maintain that the written description is adequate to show that applicants were in possession of the claimed invention. Applicants further note that, as discussed below, the specification provides working examples of agents which satisfy the requirements recited in the pending claims, namely antibodies, i.e., monoclonal antibodies, and β-chemokines.

The Examiner also stated that the disclosure fails to provide any guidance pertaining to the molecular determinants modulating NSI/SI-Env mediated events. The Examiner further stated that rational drug design is facilitated by a knowledge of those regions that are critical for envelope interactions. The Examiner asserted that in the absence of such information, the skilled artisan is essentially being asked to guess as to which agents or compounds might function in the desired manner.

In response, applicants note that in the pharmaceutical industry, "rational drug design" is not the norm. Applicants assert that, instead, the historical norm for identifying new candidate drugs is the screening of large numbers of compounds. Applicants note that, in fact, it was only as recently as the early 1990's that Agouron Pharmaceuticals, Inc. (now part of Pfizer, Inc.) successfully demonstrated the feasibility of rational drug design, i.e., using computerized models of protein molecules to systematically synthesize drugs based on those molecular structures. Applicants note further that Agouron's first commercial drug produced by rational drug design, the HIV protease inhibitor VIRACEPT® (nelfinavir mesylate), received marketing clearance from the U.S. Food and Drug Administration only as recently as 1997. Thus, applicants maintain that rational drug design is in its infancy and is today still the exception in the pharmaceutical industry. Accordingly, applicants respectfully submit that a rejection predicated on the ground that the specification does not facilitate rational drug design is without merit and should be withdrawn.

Moreover, applicants disagree with the Examiner's position that in the absence of a knowledge of those regions of an agent that are critical for interactions with the HIV envelope, guesswork is required of the skilled artisan to identify suitable agents. Applicants assert that, on the contrary, the skilled artisan is being invited to perform a routine RET screening assay as disclosed in the specification, and thereby identify agents that satisfy the requirements of the claims. Applicants maintain, therefore, that information on the molecular determinants modulating NSI/SI-Env-mediated events is not a requirement for an adequate written description of the claimed invention.

The Examiner further stated that the disclosure also fails to provide any guidance pertaining to the structure of any given "agent". The Examiner asserted that the specification provides a small number of β-chemokines that may inhibit NSI-Env-mediated events in a cell-dependent matter but that, however, no other agents or molecules meeting the requirements are disclosed. The Examiner also stated that the lack of a structural/functional correlation fails to lead the skilled artisan to any particular compound. The Examiner asserted that, accordingly, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing.

Applicants respectfully note the Examiner's above statements are in error. Applicants maintain that information on the structure of any given agent is not required because the nature of an agent which satisfies the claim requirements is result-determined, i.e., suitable agents are identified on the basis of results of the RET screening assay. Applicants remind the Examiner that the claimed invention is not directed to an agent *per se* but rather to a method of inhibiting HIV-1 fusion. This method comprises the use of an agent which is capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. Applicants note that the

specification discloses a routine, reproducible RET assay for identifying agents which exhibit these activities. Applicants emphasize, in addition, that the specification discloses four examples of monoclonal antibodies (see page 61, Table 3) which satisfy the requirements of the agent recited in the claims. Applicants note also that β-chemokines were shown to inhibit fusion of HeLa-env_{JR-FL} to a PM1 cell, but not to inhibit fusion of HeLa-env_{LAI} to a variety of CD4+ cells (see Table 4 on page 63; HeLa-CD4+ cells not specifically tested). Thus, applicants maintain that, at a minimum, the specification provides structural guidance regarding, and leads the skilled artisan to, a class of compounds that are protein moieties. In this regard, the Examiner is requested to see also new claims 14-25.

Applicants note also that the Examiner's impression that the specification discloses no agents or molecules, other than β-chemokines, which meet the requirements of the claims, is erroneous. Applicants assert that, on the contrary, the specification provides objective scientific data which demonstrate that each of monoclonal antibodies PA-3, PA-5, PA-6 and PA-7 inhibits fusion of HeLa-env_{JR-FL} to a PM1 cell (see page 60, lines 13-16 and Table 3), but does <u>not</u> inhibit fusion of HeLa-env_{LAI} to a <u>HeLa-CD4+ cell</u> (see Table 3). Applicants emphasize that these are precisely the properties of the agent recited in the pending claims.

The Examiner noted that applicants traverse the written description rejections (in their December 31, 2003 Amendment) and submit that the disclosure provides sufficient written support for the claimed invention. However, the Examiner stated that this argument is not persuasive for the reasons set forth *supra*. The Examiner further stated that, moreover, applicants' response fails to provide any objective scientific data addressing the aforementioned caveats.

In addition, the Examiner stated that the molecular determinants modulating HIV-1 envelope fusion are complex (citing O'Brien *et al.*, 1990). The Examiner further stated that the description provides a generic screening assay for identifying putative macrophage-tropic-specific or T cell-tropic-specific inhibitors. However, the Examiner asserted that this screening assay fails to provide any guidance pertaining to the structure of those compounds that can reasonably be expected to inhibit viral cell fusion. The Examiner also asserted that the skilled artisan cannot reasonably predict the structure of any given inhibitor. The Examiner further asserted that the disclosure fails to provide sufficient guidance pertaining to this point. According to the Examiner, while the disclosure describes the isolation of four MAbs (PA-3, PA-5, PA-6, and PA-7) that are capable of inhibiting envelope-mediated viral cell fusion, none of these compounds were specific to either macrophage-tropic or T cell-tropic isolates. The Examiner noted that the disclosure clearly states (citing page 60, first paragraph) that "[t]he culture supernatants from hybridomas PA-3, PA-5, PA-6 and PA-7 inhibited fusion between HeLa-env_{JR-FL} and PM1 cells in the RET assay, and also inhibited fusion between HeLa-env_{LAI} cells and certain CD4+ target cells (Table 3)." The Examiner asserted that the disclosure thus fails to identify any suitable agents with the desired properties. The Examiner further asserted that upon perusal of the disclosure, the skilled artisan would reasonably conclude that applicants were not in possession of a reasonable number of macrophage-tropic- or T cell-tropic-specific inhibitory agents. The Examiner further asserted that, finally, nothing in the disclosure points the skilled artisan toward any particular class of agents. The Examiner concluded that the rejection is accordingly proper and is maintained.

In response, applicants note that the Examiner repeats several grounds of rejection which applicants have already addressed hereinabove. However, applicants again respectfully wish to

correct the Examiner's misunderstanding that "[w]hile the disclosure describes the isolation of four Mabs (PA-3, PA-5, PA-6, and PA-7) that are capable of inhibiting envelope-mediated viral cell fusion, none of these compounds were specific to either macrophage-tropic or T-cell-tropic isolates. ... Thus the disclosure fails to identify any suitable agents with the desired properties." In this regard, applicants again direct the Examiner's attention to the experimental data which show that each of PA-3, PA-5, PA-6 and PA-7 inhibits fusion of HeLa-env_{JR-FL} to a PM1 cell (see the specification at page 60, lines 13-16 and page 61, Table 3), but does not inhibit fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell (see Table 3). Applicants note that the claimed invention recites the use of an agent which is not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. Applicants contend that the Examiner appears to have overlooked the fact that it is not fusion of HeLa-env_{LAI} to any CD4+ cell that the agent must be incapable of inhibiting, but rather, it is fusion to a HeLa-CD4+ cell. Applicants respectfully direct the Examiner's attention to page 61, Table 3 in the specification, which shows that PA-3, PA-5 and PA-7 inhibited fusion of HeLa-env_{LAI} to HeLa-CD4+ cells by 0%, and PA6 inhibited by a de minimis 7.7%. By comparison, PA-3, PA-5 and PA-6 inhibited fusion of HeLa-env_{JR-FL} to HeLa-CD4+ cells by 85, 96 and 92%, respectively, and PA7 inhibited by 67%. Thus, contrary to the Examiner's assertions, applicants maintain that the fusion-inhibitory activity of PA-3, PA-5, PA-6 and PA-7 meet the requirements of the pending claims. For the record, applicants note that the HeLa-env_{JR-FL} and HeLa-env_{LAI} cell lines used in the RET assay reflect the fusion activity of macrophage-tropic and T cell-tropic HIV-1 strains, respectively (see the specification at, *inter alia*, page 52, lines 11-33 and pages 57-59).

Thus, in response to the Examiner's statement that "the disclosure fails to identify any suitable agents with the desired properties," applicants reiterate that the specification

discloses the PA-3, PA-5, PA-6 and PA-7 monoclonal antibodies as examples of agents which meet the requirements of the agent recited in the claims. Applicants note that β-chemokines may also qualify as examples of agents that satisfy the elements of the claims (see, *inter alia*, Table 4 in the specification).

Applicants maintain that their remarks and arguments set forth hereinabove, including the identification of relevant scientific data disclosed in the specification, obviate all the grounds of the "written description" rejections stated by the Examiner. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these rejections.

Scope of Enablement

The Examiner rejected claims 7-9 and 13 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner stated that the claimed invention is directed toward methods of inhibiting macrophage-tropic HIV-1 fusion to a $CD4^+$ cell target through the administration of an agent or compound that is specific only for macrophage-tropic isolates or methods of inhibiting T cell-tropic HIV-1 fusion to a $CD4^+$ cell target through the administration of an agent or compound that is specific only for T cell-tropic isolates.

The Examiner stated that the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands,* 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The Examiner further stated that the courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary,

the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims (citing In re *Rainer,* 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965)). The Examiner also stated that the disclosure fails to provide adequate guidance pertaining to a number of these considerations as set forth below.

In response, applicants respectfully traverse the instant "enablement" rejections for the reasons set forth in detail below in addressing the specific issues raised by the Examiner. First, however, before elaborating on these specific reasons, applicants respectfully point out that the Examiner has mischaracterized the claimed invention. Applicants reiterate that the subject invention is directed to a method of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1. This method comprises contacting the CD4+ cell with an agent which is capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but which is also not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell, so as to thereby inhibit the fusion of the macrophage-tropic primary isolate of HIV-1 to the CD4+ cell. Applicants emphasize that the claimed invention does not comprise methods "methods of inhibiting T cell-tropic HIV-1 fusion to a $CD4^+$ cell target through the administration of an agent or compound that is specific only for T cell-tropic isolates," as stated by the Examiner on page 6 of the Final Office Action.

Second, notwithstanding the Examiner's statement that the courts have concluded that "several factual inquiries should be considered when making [enablement] assessments," applicants note that "it is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are illustrative,

not mandatory. What is relevant depends on the facts ..." *Amgen v. Chugai Pharmaceutical* 927 F.2d 1200, 1213 (Fed. Cir. 1991). As discussed below, applicants maintain that a sufficient number of the *Wands* factors are satisfied to establish that the specification was enabling for the inventions being claimed.

Irrespective of the number of *Wands* factors considered, applicants note that that the legal standard for a lack of enablement which emerges from *Wands*, is a requirement for undue experimentation, i.e., experimentation that is not routine. In this context, the amount of experimentation required to practice an invention is irrelevant, the critical question being whether the experimentation required is routine. See *In re Wands*, 8 U.S.P.Q.2d 1400, 1404:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. ... Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the Board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (emphasis added, footnotes omitted)

Applicants now address, in turn, each of the specific considerations of the *Wands* factors explicated by the Examiner.

1. The Examiner stated that the disclosure fails to provide adequate guidance pertaining to the molecular determinants that are specific to macrophage-tropic envelope-mediated cell fusion and T cell-tropic envelope-mediated cell fusion. The Examiner stated that rational drug development requires a knowledge of the molecular determinants that are specific to each type of virus. The Examiner also stated that this would provide a starting point for the skilled artisan to begin testing compounds in the hope of identifying something useful. The Examiner asserted, however, that the disclosure fails to provide any guidance pertaining to this consideration. The Examiner asserted, moreover, that the disclosure fails to provide a reproducible method for identifying putative inhibitors. The Examiner further asserted that whereas a fusion assay is provided in the specification, the skilled artisan cannot reasonably predict which compounds or agents will function in the desired manner.

In response, applicants reiterate that large-scale screening of compounds, rather than rational drug design is the norm in the pharmaceutical industry for identifying new drugs. Nevertheless, applicants note that the claimed methods for inhibiting HIV-1 fusion employ an agent, including a protein moiety, that binds to an antigen which is present on the surface of a PM-1 cell but which is not present on the surface of a HeLa-CD4+ cell. This antigen was later discovered by applicants to be the C-C chemokine receptor 5 (CCR5) which is the coreceptor for macrophage-tropic HIV-1 strains, but this fact was not known at the time of filing. However, although the identity of the CCR5 coreceptor was not known, the specification discloses a reproducible method for identifying agents that bind to this antigen and thereby inhibit fusion of macrophage-tropic HIV-1 strains to CD4+ cells susceptible to infection by such strains.

In this regard, applicants respectfully disagree with the Examiner's assertion that the disclosure fails to provide any guidance pertaining to a starting point for the skilled practitioner to begin testing compounds. Applicants maintain that, on the contrary, the specification provides a practicable starting point for the skilled artisan to identify a useful agent, which starting point is the performance of the RET assay. Applicants reiterate that the specification discloses the use of this assay to identify fusion-inhibitory agents which may be protein or non-protein moieties (see, *inter alia*, page 19, line 33 to page 20, line 10). As examples of protein inhibitors identified by applicants which satisfy the requirements of the claims, the specification discloses antibodies, namely monoclonal antibodies PA-3, PA-5, PA-6 and PA-7 (see page 60 and page 61, Table 3) and the β-chemokines, RANTES, MIP-1α and MIP-1β (see page 61, line 16 to page 63, line 5).

Applicants note that these disclosures of specific examples of protein moieties which inhibit HIV-1 fusion are reflected in new claims 14-25. These claims do not recite the use of a fusion-inhibitory "agent" but rather specify the use of a fusion-inhibitory "protein moiety" which may be an antibody or a β-chemokine. The antibody may be a monoclonal antibody, or an antigen-binding fragment of an antibody, or a wholly synthetic antibody or chimeric antibody or antigen-binding fragment thereof. As noted hereinabove, the specification provides explicit support for claiming these protein moieties, and further provides multiple examples of monoclonal antibodies and β-chemokines which satisfy the requirements of the claims.

In addition, applicants maintain that the specification provides an enabling disclosure for the identification of non-protein moieties which exhibit the properties of the agent recited in pending claims 7-9 and 13. In this regard, applicants note that the RET assay disclosed in the specification has been

successfully used by researchers at Hoffmann-La Roche AG ("Roche") to identify small molecule aminopiperidine derivatives that inhibit HIV-1 infection See PCT International Publication No. WO 02/079186 A2, published October 10, 2002, pages 1-3 and 59-61, attached hereto as **Exhibit A**. The stated objective of the applicant in WO 02/079186 was to identify compounds that inhibit entry of HIV-1 into target cells by binding to the CCR5 receptor, optionally without blocking chemokine binding, and thereby preventing the interaction of HIV gp120 and CD4 with this receptor. See **Exhibit A**, page 2, lines 11-15. Using the RET assay developed by applicants, numerous non-protein moieties that inhibit HIV-1 infection were successfully identified. See, **Exhibit A**, page 1, lines 2-10; page 2, line 11 to page 3, line 19; page 59, lines 18-33; page 61, lines 3-13.

Applicants note that WO 02/079186 was published after the filing date of the subject application. However, applicants emphasize that their citation of this post-filing date publication is not meant to remedy any perceived deficiency in the specification or to suggest that aminopiperidine HIV-1 inhibitors were known at the time of filing. Rather, this publication is cited as evidence that applicants' disclosures in the subject specification are sufficient to enable a person skilled in the art to identify, without undue experimentation, agents (in this case, small molecule nonpeptidyl agents) that inhibit HIV-1 infection of target cells, i.e., to demonstrate that the disclosure was enabling as of the filing date. In this regard, applicants note that post-filing date references may legitimately be used for this purpose. See, for example, *Gould v. Quigg* 3 U.S.P.Q.2d 1302, 1305 (Fed. Cir. 1987):

> As to the technical article, it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case, the later dated publication was not offered as evidence for this purpose. Rather, it was offered as evidence of the level of ordinary skill in the art at the

> time of the application and as evidence that the disclosed device would have been operative. ... It was not legal error for the district court to accept the testimony of an expert who had considered a later publication in the formulation of his opinion as to whether the disclosure was enabling as of the time of the filing date of the '540 application.

Applicants refer to the Examiner's assertions that the disclosure fails to provide a reproducible method for identifying putative inhibitors and that skilled artisan cannot reasonably predict which compounds or agents will function in the desired manner. In response, applicants maintain that the RET assay disclosed in the specification is a routine, reproducible procedure which is highly predictive for agents having the property of inhibiting HIV-1 fusion, and that undue experimentation is not required to so identify such agents. Thus, the skilled practitioner is invited to use the RET assay to screen compounds, unlimited by class and number, to reproducibly identify agents that satisfy the requirements of the claims. Moreover, applicants reiterate that multiple examples of protein moieties, i.e., antibodies and β-chemokines, which "function in the desired manner" are disclosed in the specification.

2. The Examiner stated that the disclosure fails to provide adequate guidance pertaining to the structural requirements of any given inhibitor. The Examiner stated that the disclosure fails to describe any particular class of compounds that can reasonably be expected to function in the desired manner. The Examiner also asserted that absent any guidance concerning the structure of said compounds, an undue invitation to further experimentation has been extended to the skilled artisan.

In response, applicants again emphasize that structural information on test compounds is not required to reproducibly identify HIV-1 fusion inhibitors. Applicants reiterate that an

unlimited variety of compounds, irrespective of their structural and chemical properties, can be screened using the RET assay to identify agents that satisfy the requirements of the claims. Applicants emphasize that this screening method, as disclosed in the specification, is a routine procedure that by definition does not require undue experimentation. See extract taken from *In re Wands*, 8 USPQ2d 1400, 1404, *supra*.

3. The Examiner also stated that the claims are of considerable breadth and encompass an inordinate number of compounds. The Examiner stated that, as noted *supra*, the disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating macrophage-tropic-specific and T-cell-tropic-specific fusion interactions. The Examiner further stated that the disclosure also fails to provide any guidance pertaining to the structure of any given inhibitory agent. The Examiner concluded that the specification thus clearly fails to support the breadth of the claimed invention.

In response, applicants note that whereas the RET assay may be used to screen an infinite number and variety of compounds, the agent recited in the claims must in fact satisfy well defined, specific requirements, i.e., it must be capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell. Since the claims encompass only those agents that satisfy the strict identifying characteristics and functional requirements specified, applicants maintain that the claims therefore do not encompass "an inordinate number of compounds," and are not unduly broad. Applicants reiterate that, using the RET assay, neither a knowledge of the molecular determinants modulating macrophage-tropic-specific and T-cell-tropic-specific fusion interactions, nor the structure of any given inhibitory agent, is required to identify agents that satisfy the requirements of the claims.

Applicants maintain that this position is validated by the disclosures in the specification of monoclonal antibodies and β-chemokines which satisfy these requirements. Applicants note that these two classes of agents were identified using the RET assay without any prior knowledge of the molecular determinants modulating macrophage-tropic-specific and T-cell-tropic-specific fusion interactions, or the structure of any given inhibitory agent.

4. The disclosure fails to provide a sufficient number of working embodiments. The Examiner stated that, considering the breadth of the claimed invention, a representative number of working embodiments would be required. The Examiner asserted that the specification is, however, deficient in this regard. The Examiner stated that, moreover, the disclosure clearly illustrates the problems associated with identifying specific inhibitors wherein it was reported (citing page 60, first paragraph) that "[t]he culture supernatants from hybridomas PA-3, PA-5, PA-6 and PA-7 inhibited fusion between HeLa-env_{JR-FL} and PM1 cells in the RET assay, and also inhibited fusion between HeLa-env_{LAI} cells and certain $CD4^+$ target cells (Table 3)." The Examiner concluded that, therefore, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

In response, applicants note that the specification discloses four examples of monoclonal antibodies (PA-3, PA-5, PA-6 and PA-7; see page 61, Table 3) that satisfy the requirements of an agent as recited in the pending claims. Applicants also note that three examples of β-chemokines (RANTES, MIP-1α and MIP-1β) provided in the specification also satisfy the requirements of the recited agent since these were demonstrated to inhibit fusion of HeLa-env_{JR-FL} to a PM1 cell but not inhibit fusion of HeLa-

env_{LAI} to various CD4+ cells (see pages 63-64 and Table 4; Hela-CD4+ cells not specifically tested). Applicants note that although the Federal Circuit has indicated that the presence of working embodiments is an important factor in assessing enablement, the question of how many and what kinds of examples are needed has not been definitively answered. Applicants note that, on the one hand, it has been held that disclosure of a single example is insufficient to enable a broad genus. See *In re Goodman*, 11 F.3d 1046, 1050-51 (Fed. Cir. 1993) (holding that a single example is not enough to enable a broad genus); *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (holding that a single example merely invites experimentation). On the other hand, however, the court has recently suggested that a single example is indeed enough to show enablement, provided that "any gaps between the disclosures and the claim breadth could be easily bridged." *Amgen v. Hoechst* 314 F.3d 1313, 1336 (Fed. Cir. 2003). In the context of the present application, applicants respectfully submit that the disclosure of multiple examples of antibodies and of β-chemokines in the specification is sufficient to show enablement of the claims.

Applicants also reiterate that the Examiner appears to have misunderstood the inhibitory HIV fusion activities of the PA-3, PA-5, PA-6 and PA-7 antibodies. By focusing on the statement that these antibodies "inhibited fusion between HeLa-env_{LAI} cells and certain $CD4^+$ target cells (Table 3)," the Examiner has apparently overlooked the fact that these antibodies do <u>not</u> inhibit fusion of HeLa-env_{LAI} to a <u>HeLa-CD4+ cell</u>, as evidenced by the data tabulated in Table 3 (page 61 of the specification). Thus, applicants maintain that the specification discloses a sufficient number of working embodiments of the agent recited in the pending claims to obviate any undue experimentation by a skilled artisan to practice the claimed invention.

The Examiner stated that applicants traverse and submit that the specification fully supports the breadth of the claimed

invention. The Examiner further stated that this argument is not tenable for the reasons set forth *supra*. The Examiner asserted that applicants' response fails to provide any objective scientific data that addresses the various caveats set forth. The Examiner stated that, accordingly the rejection is proper and is maintained.

In response, applicants maintain, for the reasons set forth above, that the specification does provide an enabling disclosure of the subject invention since the claims are directed to an agent having specific, well defined characteristics which are disclosed in the specification, and a routine process for obtaining agents which exhibit these characteristics is also taught in the specification. In addition, applicants have hereinabove directed the Examiner's attention to objective scientific data in the specification that addresses the issues raised. Moreover, the specification provides at least three examples of each of two classes of agents which exhibit the activities recited in the pending claims. Accordingly, applicants maintain that, based on the specification as filed, one skilled in the art would be able to make the claimed agent without undue experimentation. The Examiner is therefore respectfully requested to reconsider and withdraw the "enablement" rejections of the pending claims.

Conclusion

In view of the remarks and arguments made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the November 17, 2004 Final Office Action, and earnestly solicit allowance of all claims now pending in the subject application, namely claims 7-9 and 13-25.

Supplemental Information Disclosure Statement

This Supplemental Information Disclosure Statement is submitted under 37 C.F.R. §1.97(c)(2) to supplement the Information Disclosure Statements filed on August 14, 2002 and December 9, 2003 in connection with the subject application.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit B**), and certain of which are attached hereto as **Exhibits 1-16:**

1. U.S. Patent No. 5,994,515 A, issued November 30, 1999 to J.A. Hoxie;

2. U.S. Patent No. 6,107,019 A, issued August 22, 2000 to G.P. Allaway et al.;

3. U.S. Patent No. 6,261,763 B1, issued July 17, 2001 to G.P. Allaway et al.;

4. U.S. Patent No. 6,344,545 B1, issued February 5, 2002 to G.P. Allaway et al.;

5. U.S. Patent No. 6,759,519 B2 issued July 6, 2004 to Y. Li and S. M. Ruben;

6. W.C. Olson et al., U.S. Patent Application Publication No. 2003/0228306 A1, published December 11, 2003;

7. W.C. Olson and P.J. Maddon, U.S. Patent Application Publication No. 2004/0228869 A1, published November 18, 2004;

8. PCT International Application Publication No. WO 95/16789, published December 16, 1994 (**Exhibit 1**);

9. PCT International Application Publication No. WO 96/41020, published December 19, 1996 (**Exhibit 2**);

10. PCT International Application Publication No. WO 97/26009, published July 24, 1997 (**Exhibit 3**);

11. PCT International Application Publication No. WO 97/45543, published December 4, 1997 (**Exhibit 4**);

12. PCT International Application Publication No. WO 97/47319, published December 18, 1997 (**Exhibit 5**);

13. PCT International Application Publication No. WO 97/49424, published December 31, 1997 (**Exhibit 6**);

14. PCT International Application Publication No. WO 98/56421, published December 17, 1998 (**Exhibit 7**);

15. PCT International Application Publication No. WO 00/35409, published June 22, 2000 (**Exhibit 8**);

16. G.P. Allaway, U.S. Serial No. 08/169,311, filed December 17, 1993 (now abandoned);

17. G.P. Allaway, U.S. Serial No. 08/475,515, filed June 7, 1995 (now abandoned) (**Exhibit 9**);

18. G.P. Allaway et al., U.S. Serial No. 08/627,684, filed April 2, 1996 (now abandoned) (**Exhibit 10**);

19. G.P. Allaway et al., U.S. Provisional Application No.

60/014,532, filed April 2, 1996;

20. Allowed claims in G.P. Allaway et al., U.S. Serial No. 09/412,284, filed October 5, 1999 (**Exhibit 11**);

21. Pending claims in G.P. Allaway et al., U.S. Serial No. 09/460,216, filed December 13, 1999 (**Exhibit 12**).

22. Pending claims in G.P. Allaway et al., U.S. Serial No. 09/888,938, published October 24, 2002 as U.S. Patent Application Publication No. 2002/0155429 A1 (**Exhibit 13**);

23. Pending claims in V.M. Litwin et al., U.S. Serial No. 09/891,062; published November 29, 2001 as U.S. Patent Application Publication No. 2001/0046512 A1 (**Exhibit 14**);

24. G.P. Allaway et al., U.S. Serial No. 08/665,090, filed June 14, 1996 (now abandoned) (**Exhibit 15**); and

25. Pending claims in G.P. Allaway et al., U.S. Serial No. 09/724,105, filed November 28, 2000 (**Exhibit 16**).

The Examiner is respectfully requested to make these references of record in the present application by initialing and returning a copy of the enclosed Form PTO-1449.

Pursuant to 37 C.F.R. §1.98(a)(2), as amended in the September 21, 2004 Final Rule, copies of the above-cited U.S. Patents and patent application publications (references 1-7) are not attached hereto.

37 C.F.R. §1.98(a)(2)(iii) provides that an Information Disclosure Statement shall include, for each cited pending U.S. application, a legible copy of the application specification including the claims and any drawing of the application, or that

portion of the application which caused it to be listed including any claims directed to that portion. Under 37 C.F.R. §1.98(c), when the disclosures of two or more patents or publications listed in an Information Disclosure Statement are substantively cumulative, a copy of one of the patents or publications may be submitted without copies of the other patents or publications, provided it is stated that these other patents or publications are cumulative. In accordance with 37 C.F.R. §1.98(c), copies of certain of the references listed above are not attached hereto as they are cumulative.

Specifically, PCT International Application Publication No. WO 95/16789, published December 16, 1994 (reference 8) is a continuation of U.S. Serial No. 08/169,311, filed December 17, 1993 (now abandoned) (reference 16). Therefore, references 8 and 16 are cumulative to each other since each contains an identical disclosure. Accordingly, pursuant to 37 C.F.R. §1.98(c), a copy of reference 16 is not attached hereto.

References 18 and 19 are cumulative to each other since each contains an identical disclosure. Therefore, pursuant to 37 C.F.R. §1.98(c), a copy of reference 19 is not attached hereto.

U.S. Serial No. 09/412,284, filed October 5, 1999, is a continuation of U.S. Serial No. 08/973,601, filed March 16, 1998, which issued as U.S. Patent No. 6,261,763 B1 (reference 3). Therefore, a copy of U.S. Serial No. 09/412,284 is not attached hereto. However, in accordance with 37 C.F.R. §1.98(a)(2)(iii), a copy of the claims allowed in U.S. Serial No. 09/412,284 is attached hereto as Exhibit 11.

U.S. Serial No. 09/460,216, filed December 13, 1999, is a national stage application of PCT International Application Publication No. WO 98/56421, published December 17, 1998, (reference 14). Therefore, a copy of U.S. Serial No. 09/460,216

is not attached hereto. However, in accordance with 37 C.F.R. §1.98(a)(2)(iii), a copy of the claims pending in U.S. Serial No. 09/460,216 is attached hereto as Exhibit 12.

U.S. Serial No. 09/888,938, filed June 25, 2001 (and published October 24, 2002 as U.S. Patent Application Publication No. 2002/0155429), is a continuation of U.S. Serial No. 10/831,823, filed April 2, 1997, which issued as U.S. Patent No. 6,344,545 B1 (reference 4). Therefore, a copy of Application Publication No. 2002/0155429 is not attached hereto. However, in accordance with 37 C.F.R. §1.98(a)(2)(iii), a copy of the claims pending in U.S. Serial No. 09/888,938 is attached hereto as Exhibit 13.

U.S. Serial No. 09/891,062, filed June 25, 2001 (and published November 29, 2001 as U.S. Patent Application Publication No. 2001/0046512), is a continuation of 09/118,415, filed June 17, 1998, a national stage application of PCT International Application Publication No. WO 97/26009, published July 24, 1997 (reference 10). Therefore, a copy of U.S. Serial No. 09/891,062 is not attached hereto. However, in accordance with 37 C.F.R. §1.98(a)(2)(iii), a copy of the claims pending in U.S. Serial No. 09/891,062 is attached hereto as Exhibit 14.

U.S. Serial No. 09/724,105, filed November 28, 2000, is a continuation of U.S. Serial No. 08/874,618, filed June 13, 1997, which has the same disclosure as PCT International Application Publication No. WO 97/47319, published December 18, 1997 (reference 12). Therefore, a copy of U.S. Serial No. 09/724,105 is not attached hereto. However, in accordance with 37 C.F.R. §1.98(a)(2)(iii), a copy of the claims pending in U.S. Serial No. 09/724,105 is attached hereto as Exhibit 16.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number

provided below.

Pursuant to 37 C.F.R. §1.97(c)(2) and 1.17(p), a fee of one hundred and eighty dollars ($180.00) is required for filing the enclosed Supplemental Information Disclosure Statement. A fee of one hundred and eighty dollars ($180.00) is also deemed necessary in connection with the filing of multiple dependent claims in this Amendment. Accordingly, a check in the total amount of THREE HUNDRED AND SIXTY DOLLARS ($360.00) is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

John P White 1/18/05

John P. White Date
Reg. No. 28,678